REMARKS

Claims 1-3, 9-19, 41, and 43-59 are currently pending and under examination in the instant application. By this Amendment, claim 1 has been amended to recite that the nucleotide sequence coding for the transporter domain is located downstream from the nucleotide sequence encoding the passenger protein. Support for the amendment to claim 1 can be found, *inter alia*, in the specification at page 19. Applicants are concurrently submitting corrected formal drawings as required by the Examiner. Applicants assert that neither the claim amendment nor the submission of corrected drawings introduces any new matter. Accordingly, their entry is requested.

Applicants gratefully acknowledge the Examiner's withdrawal of the objections to the specification and the rejections of the claims based on the Amendment of June 3, 2002 as follows:

rejection of claims 1-3, 9-19 and 41-59 under 35 U.S.C. §112, second paragraph;

rejection of claims 41-59 under 35 U.S.C. §112, second paragraph;

rejection of claims 1-3, 9 and 15-19 under 35 U.S.C. §102(b);

rejection of claims 1-2, 9 and 15-19 under 35 U.S.C. §102(e); and

rejection of claims 1-3, 9-19 and 41-59 under 35 U.S.C. §103(a).

I. Examiner's Rejection of Claims 1, 2, 9, 10 and 15-19 under 35 U.S.C. §102(b)

The Examiner rejected claims 1, 2, 9, 10, and 15-19 under 35 U.S.C. §102(b) as allegedly being anticipated by Georgiou (USPN 5,348,867).

The Examiner relied on Georgiou for disclosing a method for expressing recombinant bacterial proteins on a host cell surface where the proteins are encoded by a vector having a tripartite chimeric gene comprising a targeting DNA sequence, a traversing sequence and a DNA for a desired protein. The Examiner considers a protease recognition domain intrinsic to the outer membrane proteins.

In response, Applicants assert that the amendment to claim 1 obviates the Examiner's rejection. Georgiou discloses a tripartite chimeric gene subcloned into a vector. In column 4, lines 33-35, Georgiou describes the chimeric gene as having a segment that encodes a desired polypeptide, the segment being positioned downstream from a segment encoding a transmembrane sequence. The Examiner regards the "desired polypeptide" as corresponding to Applicants' passenger polypeptide and the transmembrane sequence to be equivalent to Applicants' transporter domain.

The Applicants' claimed process is not anticipated by Georgiou because Georgiou does not disclose a polynucleotide comprising a nucleotide sequence that encodes a transporter domain located downstream from a nucleotide sequence that encodes a passenger peptide. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1, 2, 9, 10, and 15-19 under 35 U.S.C. §102(b).

II. Examiner's Rejection of Claims 1, 2, 9, 10 and 15-19 under 35 U.S.C. §102(b)

The Examiner rejected claims 1, 2, 9, 10, and 15-19 under 35 U.S.C. §102(b) as allegedly being anticipated by Klauser (EMBO J. 9:1991-1999 (1990)).

The Examiner relied upon Klauser for teaching a recombinant expression vector containing gene fragments encoding in the following order:

vector-promoter-signal peptide-passenger protein-protease recognition site-linker-transmembrane domain.

Klauser describes this vector as being in the form of a "translocation-competent" conformation.

Applicants respectfully traverse the Examiner's rejection. Applicants submit that the Klauser reference cited by the Examiner against the claims in the present Office Action is equivalent in content to U.S. Patent No. 6,040,141 (hereinafter "'141"). The Examiner had previously cited the '141 patent against the claims (see Office Action of January 3, 2002), then withdrew the rejection based on Applicants' arguments filed in the Amendment of June 3, 2002. Applicants respectfully direct the examiner's attention to the comments presented in that Amendment.

Additionally, Applicants reiterate that the increased expression of choleratoxin B subunit for the inventive process is achieved without lysing the host cell, and that these results are unexpected and improved over the process of Klauser (MPEP §716.02(b)). The Examiner's attention is directed to Example 2 in the present specification where the inventive process is compared with the process of Klauser. This improved property for the inventive process is attributable to the transporter domain being homologous with respect to the host cell type. In contrast, Klauser relies on a heterologous transporter domain with respect to the host cell. Applicants maintain that these data are dispositive

to the Examiner's position that Klauser teaches a process similar to the present claimed invention.

Accordingly, Applicants assert that the claims of the instant invention are patentably distinguishable over Klauser, and respectfully request reconsideration and withdrawal of the rejection.

III. Examiner's Rejection of Claims 1-3, 9, 10, 41 and 43-59 under 35 U.S.C. §103(a)

Claims 1-3, 9, 10, 41 and 43-59 are rejected under 35 U.S.C. §103(a) as being obvious over Klauser in view of Benz (Molec. Biol. 6:1539-1546 (1992)).

In response, Applicants respectfully traverse the Examiner's rejection. Applicants first direct the examiner's attention to the comments set forth above with respect to the Klauser reference. The Examiner considers that Klauser is silent with respect to the process having a vector containing a gene fragment encoding the AIDA-I protein as the transporter component of the chimeric gene, and relies upon Benz for this disclosure.

a) Claims 1-3, 9 and 10 (process for transfecting a bacterial host cell)

Applicants submit that claims 1, 2, 9, and 10 are not obvious over Klauser as a primary reference for the reasons previously discussed. Because Klauser fails as a primary reference to teach the invention of Claims 1, 2, 9, and 10, it follows that Benz does not cure the deficiencies of Klauser.

Furthermore, Benz does not disclose an AIDA protein to be an autotransporter. Benz merely demonstrates preliminary evidence that a C-terminal 45 kDa portion of the immature AIDA-1 is necessary for correct maturation of the AIDA-1 protein. The function of the 45 kDa protein, however, is not known (see Benz, page 1539). Accordingly, the data in Benz are not substantive proof that the cleavage step is part of the transport mechanism. Benz does not teach or suggest that the 45 kDa protein is a transporter capable of transporting a passenger protein through the outer membrane of a gram-negative bacterium.

Rather, Benz teaches away from the instant claimed autotransporter. Benz demonstrates a second protein (ORF A) encoded by an open reading frame upstream from the AIDA gene (see, for example, Figure 1, page 1540), which is involved in the expression of a mature and biologically active form of the AIDA-1 protein (see page 1544). Thus, one skilled in the art relying on the disclosure of Benz would have concluded that both the ORF A protein **and** the 45 kDa protein are required for expression of mature AIDA-1 (or at least that the 45 kDa fragment alone would not have been sufficient for expression). This is in direct contrast to the teaching of Pohlner et al. (1987) who describe the maturation of Neisseria IgA protease involving proteolytic cleavage.

Thus, one skilled in the art would not have had a reasonable expectation that the addition of the 45 kDa protein of Benz to the expression system of Klauser would have resulted in the presentation of passenger peptides on the surface of gram-negative

bacterium. Accordingly, the instant claimed process is not taught or suggested by Klauser either alone, or in combination with Benz.

b) Claims 41 and 43-54 (process for making a bacterial library)

Claims 41 and 43-54 are directed to a process for making a library where the vector has the following conformation:

vector-signal peptide-passenger peptide-AIDA transporter domain.

Because neither Klauser nor Benz disclose that an AIDA protein is an autotransporter, one of ordinary skill in the art would not have been motivated to combine the reference disclosures in the manner asserted by the Examiner. Even combining the references as the Examiner has, one would not have achieved the claimed invention. Accordingly, Applicants respectfully request withdrawal of this ground of the Examiner's rejection.

c) Claims 55 and 56-59 (a recombinant vector and bacterium transfected with the vector, respectively)

Claims 55 and 56 are directed to vector and a bacterial cell transfected with the vector where the vector has the following conformation:

vector-signal peptide-passenger peptide- transmembrane linker- AIDA transporter domain.

Because neither Klauser nor Benz disclose that an AIDA protein is an autotransporter, one of ordinary skill in the art would not have been motivated to combine the reference disclosures in the manner asserted by the Examiner. Even combining the references as the Examiner has, one would not have achieved the

claimed invention. Accordingly, Applicants respectfully request withdrawal of this ground of the Examiner's rejection.

IV. Examiner's Rejection of Claims 1-3, 9, 10, 41-53 and 55-59 under 35 U.S.C. §103(a)

The Examiner rejected claims 1-3, 9, 10, 41-53 and 55-59 under 35 U.S.C. §103(a) as allegedly being obvious over Georgiou in view of Benz.

In response, Applicants respectfully traverse the Examiner's rejection. Applicants direct the Examiner's attention to the comments set forth above with respect to Georgiou. The Examiner considers Georgiou silent with respect to the process having a vector containing a gene fragment encoding the AIDA-I protein as the transporter component of the chimeric gene, and relies upon Benz for this disclosure.

a) Claims 1-3, 9 and 10 (process for transfecting a bacterial host cell)

Applicants submit that claims 1, 2, 9 and 10 are not obvious over Georgiou as a primary reference for the reasons previously discussed under section I of this response. Because Georgiou fails as a primary reference to teach the invention of Claims 1, 2, 9 and 10, it follows that Benz does not cure the deficiencies of Georgiou. For purposes of brevity, Applicants incorporate their comments with respect to the patentability of the claims over Benz as set forth under section III. a.

Applicants submit that Georgiou and Benz do not teach or suggest the process invention as a whole (MPEP §2143.01) or provide objective reasons for modifying the disclosed process to obtain the inventive process utilizing the recombinant vector as presently claimed (MPEP §2143.01). The Examiner is respectfully requested to

consider and enter all of the foregoing arguments and to withdraw the rejection based thereon.

b) Claims 41 and 43-54 (process for making a bacterial library)

Applicants submit that Georgiou in combination with Benz does not teach the inventive vector, and thus not the process using the vector to obtain a recombinant bacterial library. In fact, one skilled in the art would have considered that Georgiou actually teaches way from the inventive chimeric vector. Accordingly, one skilled in the art would not have had any apparent motivation to combine the references in the manner asserted by the Examiner.

c) Claims 55 and 56-59 (a recombinant vector and bacterium transfected with the vector, respectively).

Applicants submit that Georgiou in combination with Benz does not teach the inventive vector much less a recombinant bacterial cell. In fact, one skilled in the art would have considered that Georgiou actually teaches way from the inventive chimeric vector. Accordingly, one skilled in the art would not have had any apparent motivation to combine the references in the manner asserted by the Examiner.

V. Examiner's Rejection of Claims 1-3, 9-19, 41, 43-53 and 55-59 under 35 U.S.C. §103(a)

The Examiner rejected claims 1-3, 9-19, 41, 43-53 and 55-59 under 35 U.S.C. §103(a) as being obvious over Georgiou, in view of Benz for claims 1-3, 9, 10, 41, 43-53 and 55-59 and further in view of Kozono (Nature 39 (1994)) for claims 11-19.

The Examiner considers Claims 1-3, 9-19, 41, 43-53 and 55-59 *prima facia* obvious over Georgiou in view of Benz and Kozono.

In response, Applicants respectfully traverse the Examiner's rejection. Applicants direct the Examiner's attention to the comments set forth above with respect to Georgiou and Benz. The Examiner considers that Georgiou and Benz are silent with respect to the process having a vector containing a gene fragment encoding an antibody or antigen-binding domain as the passenger protein component of the chimeric gene, and relies upon Kozono for this disclosure.

Applicants submit that claims 1-3, 9, 10, 41, 43-53 and 55-59 are not obvious over Georgiou as a primary reference for the reasons previously discussed under section I of this response. Because Georgiou fails as a primary reference to teach the invention of Claims 1-3, 9, 10, 41, 43-53 and 55-59, it follows that Benz does not cure the deficiencies of Georgiou, as discussed. For purposes of brevity, Applicants incorporate their comments with respect to the patentability of the claims over Benz as set forth under section III. a.

With respect to the Examiner's rejection of Claims 11-19 over Kozono, Applicants traverse for the following reasons.

Kozono describes fusion proteins between MHC Class II proteins and a peptide attached by a flexible peptide linker. This covalent peptide-MHC complex is recognized by specific T-cell receptors. The fusion proteins of Kozono could be used as passenger proteins and expressed on the surface of E. coli as discussed in the specification on page 27. Accordingly, Kozono does not teach or suggest the essential features of the

invention, and therefore, the reference does not cure the deficiencies of Georgiou and Benz with respect to claims 11-19. The Examiner is respectfully requested to consider and enter all of the foregoing comments and to withdraw the rejection based thereon.

In view of the above remarks and amendment to claim 1, Applicants believe that the Examiner's objection to the drawings and rejections of the claims set forth in the August 23, 2002 Office Action have been overcome and that the present application is in condition for allowance. The Examiner is invited to telephone the undersigned if it is deemed to expedite allowance of the application.

Respectfully submitted,

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Enclosure: Marked-up Copy of Amended Claim 1

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MARKED-UP COPY OF AMENDED CLAIM 1

1. (Twice Amended) A process for presenting passenger peptides or polypeptides on the surface of Gram-negative host bacteria, comprising

a) providing a host bacterium transformed with a vector encoding a polynucleotide operatively linked to a promoter, wherein said polynucleotide comprises:

(i) a nucleotide sequence encoding a signal peptide,

(ii) a nucleotide sequence encoding a passenger peptide or polypeptide,

(iii) a nucleotide sequence encoding a protease recognition site,

(iv) a nucleotide sequence encoding a transmembrane linker, and

(v) a nucleotide sequence encoding a transporter domain of an autotransporter,

wherein the nucleotide sequence encoding the transporter domain is located downstream from the nucleotide sequence encoding the passenger peptide or polypeptide; and

b) cultivating the host bacterium under conditions for inducing expression of the polynucleotide and presentation of the passenger peptide or polypeptide of step (ii) on the surface of the host bacterium, wherein the passenger peptide or polypeptide of step (ii) is heterologous in relation to the transporter domain of step (v), and the host bacterium is homologous in relation to the transporter domain of step (v).